

al. taken with Dougherty et al.

Also submitted herewith is a Supplemental Information Disclosure Statement, which the Examiner is hereby requested to consider and make of record in the present application. The following documents are referred to in order to provide a better picture of the state of the art which informed the Waterhouse and Wassenegger reviews. These are the actual documents cited in the reviews in alleged support of hypothetical small cRNAs or asRNAs.

English et al (1996) Plant Cell 8: 179-188 (21 in Wassenegger)
Lindbo et al (1993) Plant Cell 5: 1749-1759 (39 in Wassenegger) - already cited in original IDS

Prins & Goldbach (1996) Arch Virol 141: 2259-2276 (55 in Wassenegger)

Sijen et al (1996) Plant Cell 8: 2277-2294 (66 in Wassenegger)
Smith et al (1994) Plant Cell 6: 1441-1453 (67 in Wassenegger)
Elmayan & Vaucheret (1996) Plant J 9: 787-797 (20 in Wassenegger)
Baulcombe & English (1996) Curr Opin Biotech 7: 173-180 (7 in Wassenegger)

Mezlaff et al (1997) Cell 88: 845-854 (45 in Wassenegger) already cited in original IDS

Kunz et al (1996) Plant J 10: 437-450 (38 in Wassenegger)
Van Blokland & Van der Geest (1994) Plant J 6: 861-877 (75 in Wassenegger)

Schiebel et al (1993) J Biol Chem 268: 11851-11857 (6 in Waterman)
Schiebel et al (1993) J Biol Chem 268: 11858-11867 (7 in Waterman)

Baulcombe (1996) Plant Cell 8: 1833-1844 (4 in Waterman)
Lindbo & Dougherty (1992) Mol Plant-Microbe Interac 5: 144-153 (2 in Waterhouse)
Lindbo & Dougherty (1992) Virology 189: 725-733 (3 in Waterhouse)

Stam & Kooter (1997) Ann Bot 79, 3-12 (5 in Waterhouse).
The following documents are provided in order to provide a picture of the state of the art after the publication of the present invention:

Elbashir et al (2001) Nature Vol 411, 24 May 2001: 494-498;
Waterhouse et al (2001) Trends in Plant Science Vol 6. No 7:
July 2001: 297-301 and WO 01/75164.

All of the foregoing newly cited references are also listed in the accompanying PTO 1449 form, submitted herewith.

Applicants respectfully submit that the present claims are in condition for allowance. Each of the above-noted objections and rejections under 35 U.S.C. §102(a), and §103 is, therefore, respectfully traversed for the reasons set forth below.

**THE INVENTION CLAIMED IN CLAIMS 1, 5-10, 12-17, 21, 26-29, AND
32-34 IS NOT ANTICIPATED BY THE DISCLOSURE AT THE MEETING IN
LEYSIN SWITZERLAND AS THIS PRESENTATION WAS THE RESULT OF THE
COLLABORATIVE WORK OF BOTH INVENTORS**

Claims 1, 5-10, 12-17, 21, 26-29 and 32-34 have been rejected under 35 U.S.C. §102(a) as allegedly anticipated by the presentation made by one of the inventors in Leysin, Switzerland. Applicants respectfully submit that the subject matter presented at the meeting in Switzerland was the result of the joint efforts of both named inventors. As the Examiner is aware, only a single inventor/speaker can present the results of a collaborative work at a scientific meeting. Provided herewith is a copy of the abstract upon which the presentation was based. The Examiner's attention is directed to the fact that both Drs. Hamilton and Baulcombe are listed as co-authors. A Declaration attesting to the fact that the subject matter presented was the result of a joint inventive effort is also provided in support of Applicant's position.

Additionally, as mentioned previously, a certified copy of the priority document is submitted herewith thereby perfecting Applicant's priority claim.

In light of the Abstract and Declaration evidence presented herewith, and the submission of the certified priority document, Applicants submit that the Examiner is in error regarding his assertion that the meeting presentation was made by a different inventive entity than that set forth in the present application. Accordingly, the rejection of claims 1, 5-10, 12-17, 21, 26-29, and 32-34 is inappropriate and should be withdrawn.

THE COMBINED DISCLOSURES OF WATERHOUSE ET AL. AND WASSENEGGER ET AL. FAIL TO RENDER THE SUBJECT MATTER CLAIMED IN CLAIMS 1, 2 5-17, 21, 26-29 AND 32 OBVIOUS

The Examiner has rejected claims 1, 2, 5-17, 21, 26-29 and 32 as allegedly obvious over the combined disclosures of Waterhouse et al. and Wassenegger et al. taken with Dougherty et al. The Examiner asserts that the rejection has been maintained for the reasons set forth in the Official Action mailed June 21, 2001 on page 5-10. At the outset, Applicants respectfully submit that Figures 3 and 5 of Waterhouse et al. depict the mRNA encoded by the transgenes introduced into the tobacco plants. These RNAs do not correspond to the short RNA molecules which are 21-25 nucleotides in length which are responsible for post transcriptional gene silencing in plants. Figure 3 depicts a Northern blot which merely shows that the plants expressed appropriate mRNA levels of the transgene. Figure 5 shows mRNA levels in progeny of the transgenic plants shown in Figure 3. There is no teaching or suggestion whatsoever in this reference regarding the presence of the short RNA molecules of Applicants claims which are responsible for post-transcriptional gene

silencing.

The Examiner relies on Wassenger et al. for the teaching that a 43 nucleotide long element forms a double-stranded structure with the coding region of the petunia chalcone synthase gene. Thus, there is no small RNA molecule described in this system. This 43 nucleotide element resides at the 3' end of the chalcone synthase mRNA molecule which is significantly larger than 43 nucleotides. The element "folds back" to hybridize with the coding region. The double stranded structure is then cleaved by endonuclease at a preferential site. The actual text reads as follows "Subsequently two RNA molecules would be released that "could have the potential" to base-pair with function chalcone synthase mRNAs again". Thus, a careful reading of this reference fails to provide the suggestion that small RNA molecules are mediating gene silencing in plants. Indeed, at page 352, first column, Wassenger et al. acknowledge that "the nature of the aberrant RNAs (depicted in Figure 1) is unknown".

Regarding the Examiner's assertion that Wassenger et al. suggest that homology of 60-130 bp between the inactivating transgene and a target sequence can lead to PTGS, again, this is homology between much longer sequences. This sentence does not relate to small, discrete RNA molecules between 21-25 nucleotides in length. Wassenger et al. refer to Dougherty et al. for the premise that small RNAs 10-100 nt in length can be produced by RdRP in plants. However, at the beginning of the same paragraph Wassenger et al. note that these postulated RNA molecules "should have been detectable" **BUT WERE NOT**.

At page 7 of the Official Action, the Examiner asserts that Dougherty et al. teaches that "short oligonucleotides (10-40 nucleotides) can produce antisense RNA molecules that hybridize with a target RNA molecule to form double stranded RNA molecules. Again, Applicants respectfully submit that the Examiner is

erroneously interpreting this reference. The heading of the cited paragraph is "Suppression mediated by antisense oligonucleotides". These antisense DNA molecules are introduced into cells and hybridize with the target molecule. They are certainly not capable of "producing" antisense RNA as asserted by the Examiner. The Examiner's reliance on the disclosure of the *lin-14* transcripts in *C. elegans* is misplaced as Applicants claims are directed to plants. Furthermore, these transcripts are "proposed to bind the repeat sequences in the 3' untranslated region". This teaching is mere speculation and cannot provide the requisite teaching leading one of ordinary skill in the art to applicants invention.

The present application is based on the work done by the inventors demonstrating for the first time that SRMS (short sense and anti-sense RNA molecules of about 25 nt in length associated with PTGS) existed, that they were of a defined range of lengths, and that they could be detected in organisms that exhibit PTGS (page 2).

The invention therefore definitively resolved years of uncertainty as to whether such molecules even existed, what size they were, and whether they could be detected.

In alleging that the claimed subject matter is obvious over the prior art, Applicants respectfully submit that the Examiner erred in:

- (i) Overestimating the disclosure of hypotheses in "review" articles in favour of actual scientific publications upon which they were based, and/or,
- (ii) Overestimating the skill of skilled person (making them "ingenious" in the words of the prior art reviews),
- (iii) In selectively picking wording from prior art reviews rather than reading the documents as a whole, and thereby ignoring the fact the documents themselves would not have led to

a reasonable expectation of success in arriving at the instant invention, and

(iv) Ignoring other indicia of inventive activity i.e. the chronology of the documents involved, the publication (after filing) of the invention in "Science", and the subsequent acknowledgement of the "Science" publication by other workers in the field as being the first disclosure of the existence of SRMs in higher plants.

As mentioned previously, the Examiner has relied on the following documents in support of the final rejection of claims: Waterhouse et al. (1998); Wassenegger et al. (1998) and Dougherty & Parks (1995).

In essence, the Examiner states that the various comments in Dougherty & Parks (1995) relating to RNA molecules (both hypothetical and actual, in a variety of contexts) would have led one of ordinary skill in the art to modify the teachings of Waterhouse et al (1998) and Wassenegger et al (1998) thereby arriving at the present invention, which was itself an art-recognized goal.

Obviousness under 35 U.S.C. 103 is a question of law. An analysis of non-obviousness must be based on several factual inquiries:

- (1) the scope and content of prior art;
- (2) the differences between the prior art and the claims at issue,
- (3) the level of ordinary skill in the art at the time the invention was made, and (4) objective evidence of non-obviousness, if any. Graham v. John Deere Co, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966).

(1) The scope and content of prior art

It should be stressed that the documents cited herein, and

the sections of them referred to, have been selected (*ex post facto*) to be those most relevant as background to the invention, in order to demonstrate that even this springboard does not render the present claims obvious. However, for completeness it must be remembered that there was also a great deal of literature in the field of gene silencing which was completely silent on the subject of RNA interference, and thus the true state of the art would have presented the person of ordinary skill in the art with even less expectation that SRMs actually existed in a detectable form.

It should firstly be noted that Waterhouse (1998) and Dougherty & Parks (1995) are reviews, which is to say that they contain no original scientific evidence, but merely present summaries of earlier disclosures, and suggest a variety of, often conflicting, hypotheses based on them. By definition they cannot resolve technical questions in the art - quite the opposite in fact, they can only pose questions and highlight technical problems.

The useful arts are promoted by answering these questions and solving these problems. To quote Dougherty & Parks (1995) below when referring to the cRNAs depicted in Figure 1 of that review:

"**Demonstration** of their **existence** and function [of cRNAs] could revolutionize our view of gene regulation" (emphasis added). See page 404. Secondly, it is well-established that: "it is not permissible to pick and choose only so much of any given reference as will support a given position and ignore the reference in its totality." *In re Umbricht*, 160 USPQ 15 (CCPA 1968).

Although references 3 and 4 to Lindbo et al. and Baulcombe cited in Waterhouse dissect out a number of references to RNA molecules **in general** having a variety of size ranges (e.g. 43,

60-130, 10-100, 10-20, 21 or 69, 10-75 etc.) in many cases a close scrutiny of the context in which they appear shows that they do not even refer to discrete RNA molecules produced in the PTGS process, hypothetical or otherwise.

The three documents relied on by the Examiner in support of the §103 rejection and the references cited therein are discussed below in chronological order.

Dougherty & Parks (1995)

This is a review which "develops a hypothesis that suggests" a single cellular mechanism for both anti-sense and sense suppression.

Paraphrasing, Dougherty et al. discuss, *inter alia*:

(i) Suppression mediated by introduced anti-sense molecules (10-40 nts - see page 399). Note that this section has nothing to do with the present invention whereby natural SRMs are created *in situ* rather than introduced. Indeed, the oligonucleotides discussed at this section of the reference are DNA rather than RNA.

(ii) Natural anti-sense molecules in prokaryotes which are transcribed from DNA (67-175 nts - pg 400, Co 1).

(iii) Transgenic antisense in eukaryotes: this is actually transcribed from DNA (300 nts - pg 400, Co 2).

(iv) Four proposed mechanisms of sense suppression of gene expression (pg 400, Co 2 - pg 401, Co 1). These include transcription to anti-sense by fortuitous promoters, decrease in transcription analogous to paramutation i.e., DNA:DNA interaction, methylation and PTGS.

On page 401, "possible" modes of action are discussed. In

relation to one of these i.e., that recognition comes from sRNAs (pg 402, Co 1) the review cites [34] which is Lindbo et al., which is already of record in this application.

Lindbo et al. include experimental data but despite including nuclear run-off assays and an analysis of mRNA it absolutely does not demonstrate or suggest detection of any short RNA species. The Discussion (pg 1756) refers to putative defective interfering RNAs (DI RNA) from Brome Mosaic Virus (BMV) and notes that "[BMV DI RNA] analysis **may** provide the insight into the **length** and **composition** of the sequences needed to elicit the putative cellular response" (emphasis added).

On page 402, Dougherty et al. note the existence of a plant RdRP and cite references 42, and 43 to Schiebel et al. who state that RdRP could produce cRNAs of 10-75 nucleotides in **cell-free** studies, however this should not be taken out of context since it gives no indication of the template or product size *in vivo*.

Indeed, on reviewing the Scheibel et al. references, it can be seen that these are experimental disclosures of the purification and activity of purified RdRP - they are not in any way related to gene silencing and furthermore, a cellular role for the enzyme was unresolved in the papers.

Figure 1 on page 402 of Dougherty et al. is a schematic portrayal of an RNA driven model. Clearly, Dougherty et al. were not sure of the putative length of the SRMS responsible for gene silencing or whether or not such molecules existed as set forth at page 404. Indeed, these small cRNA as described as ">10 nt?" to "<20 nt?".

Wassenger et al. (1998)

On page page 350, column 2 of Wasseneger et al. it is stated that a "According to several models on RmVR...short antisense RNA molecules" are produced. The references cited in support of this

[21,39,55,66,67] are as follows:

Reference 21 by English et al. has as a co-author one of the present inventors. Although some experimental data is presented in this reference, there is no data on short RNA molecules or any length attributed to them. At page 186, final paragraph before the "Methods" heading, these authors disclose that aRNA and asRNAs are "elusive components" of the model which "may be difficult to detect". A "search" for them is the next step.

Reference 39 to Lindbo et al. is discussed above. Reference 55 to Prins et al. is a Review. It is silent on the detection of short RNAs.

Reference 66 to Sjien et al. discloses experimental results including several RNA gel blots and nuclear run on. No detection of short RNAs is disclosed. Reference 67 to Smith et al. discloses experimental results and again RNA is analysed. However there is no detection of short RNAs. On pg 1449 there is clearly doubt "if these **hypothetical** small complementary RNAs accumulate..." (emphasis added)

Further down the page the Wassenegger review refers to reference [20] to Elmayan et al. These authors disclose experimental results including RNA analysis. There is no detection of short RNAs. Several hypotheses are listed on pg 795.

As mentioned previously, the next section of Wassenegger et al (1998) notes that Mezlaiff and co-workers reported that the Chs gene could be silenced via an RdRP independent mechanism. However, as set forth above, this 43 nucleotide element of the 3' region is simply a region of self-complementarity (see Fig 5, 5' to 3') to the coding sequence. This disclosure has nothing to do with discrete, short RNA molecules.

The most relevant section of Wassenegger et al (1998) to the present invention is "Detection..." on page 356 but again this

leaves no more than an unanswered questions.

Wassenegger et al. state the various RNA species "**Should have** been detectable" (emphasis added) but acknowledges (page 356, column 1, lines 14 - 15) that "there is no experimental evidence of RdRP-synthesized antisense RNA in plants." It refers to [17,39] as apparently proposing 10-100 nt size range for RdRP-produced RNA. These are Dougherty & Parks (1995) and Lindbo et al. which are discussed above, and in fact do not teach this range at all. On page 356, column 1, lines 20 - 22 it is stated:

"an apparent requirement of transgene RNA does not mean that a corresponding asRNA (antisense RNA) is produced"

In terms of actual detection of asRNAs (of any length) only those directly transcribed from genomic DNA had been detected. References 38 to Kunz et al. and 75 to Van Blockland et al. are cited for this disclosure. In Kuntz et al. the strengths and weaknesses of the RdRP model are discussed. Interestingly, these theories are mooted at page 447 (12th line from bottom) where it is taught that the activator may be consumed as part of the degradation process i.e., it would not even be detectable.

Van Blockland et al. disclose experimental results, including AS transcripts in nuclear run-on. These are assumed to result from ectopic expression.

As pointed out in Applicants' previous response, Wassenger et al. teach that

"further ingenious experiments will be needed to puzzle out, how...asRNA can be determined".

On page 360, Wassenegger et al conclude as follows:

"much more effort is needed to detect abRNA, Rt RNA and asRNA."

Waterhouse et al. 1998

This is an actual research paper based on expression of

sense and antisense RNA.

On page 13959, Waterhouse et al. state that it has been suggested that transgene PTGS is effected by small cRNAs. The papers cited in support of this (6,7) are the Scheibel et al. references discussed above, relating to purified RdRP. These references are not concerned with silencing. Waterhouse et al. further state that the "hypothetical" cRNAs act by hybridization (4). This reference is a review article by Baulcombe et al. and contains no evidence of the existence of small asRNA other than noting the existence of the RdRP described by Scheibel et al.

In the discussion section, at page 13692, column 1, (first 6 lines) it is noted that there are a number of models proposed for the induction and operation of PTGS but none completely fit the observed results. In reference to the idea that an RdRP makes complementary strands and that these potentiate degradation of the target RNA, three references are cited (2,3,19) which are Lindbo and Dougherty MPMI (1992), Lindbo and Dougherty J. Vir. (1992) and Dougherty & Parks (1995).

Lindbo and Dougherty, MPMI (1992) disclose experiments concerned with coat protein resistance. Northern blots are shown but nothing concrete is disclosed about the mechanism of resistance, and certainly nothing about short RNAs.

Lindbo and Dougherty J. Vir. (1992) is also concerned with coat protein resistance and also shows some Northern blotting data. Again the results seem to be attributed to some kind of direct anti-sense activity. There is no suggestion of short RNAs.

Waterhouse et al. further disclose at page 13692, column 2, lines 4 - 6) that "in most models, the anti-sense RNA or cRNA is proposed to hybridize with the target RNA in some way marking it for degradation (4,5,19)" Reference 4 of Baulcombe et al. has been discussed above. Reference 5 is Stam and Kooter and

reference 19 is Dougherty & Parks (1995).

Stam and Kooter is a review article. At page 8, column 1, paragraph 4), these authors acknowledge "we can only speculate" about the nature of the RNA degradation activity in PTGS, before going on to discuss some of the references cited above.

On pages 13963-64 and Fig 7 Waterhouse generally repeat the earlier model of Dougherty & Parks (1995).

Conclusions on the scope and content of the prior art:

It is clear from the discussion above that in 1999 there was still great uncertainty about the mechanism by which PTGS progressed.

It is acknowledged by the applicant that the existence of RNA species (derived from RdRP and associated with PTGS) had been tentatively hypothesized, amongst other models, from as early as 1992.

However no document in the prior art categorically demonstrated that such RNA species (of any length) actually existed in a PTGS context.

Even if such species were assumed to exist there was no clear suggestion in the prior art as to what size they would be. Suggestions in the art mostly refer back ultimately to Dougherty & Parks (1995) which puts a tentative 20 nt upper limit on them.

Importantly, it is clear from the above that those skilled in the art considered that the detection of these molecules was likely to be problematic, with the result that, although the workers in the field in numerous cases from 1992 to 1999 ran nuclear run-on experiments, and performed Northern blots, none of them actually detected, or apparently even tried to detect, short RNA species. This notwithstanding that it was also acknowledged in the art that the detection of such species would be an

important step in understanding PTGS.

(2) The differences between the prior art and the claims at issue,

By contrast with the manifest uncertainty in the prior art, the present application teaches:

- (i) SRMS exist, and that they are both sense and antisense
- (ii) that they are about 25 nt in length (e.g. within 5 nt of this)
- (iii) that, contrary to the prior art, they are actually detectable in organisms that exhibit PTGS (page 2)

The claims reflect this contribution to the art i.e. the first detection and analysis of SRMs. More specifically the claims are as follows:

Claims 1, 5-11, 21, and 32-34 drawn to a method determining occurrence of gene silencing using SRMS;

Claim 12-17 drawn to a preferred processes for isolating SRMS;

Claims 26-28 drawn to DNA constructs, host cells, and plants employing SRMS based materials; and

Claim 29 drawn to methods of silencing using such DNA constructs.

(3) The level of ordinary skill in the art at the time the invention was made

As stated above, there were clear deficiencies in the art in

relation to providing definitive evidence about the existence and nature of the putative RNA molecules. However,

"[W]hile the deficiencies in the prior art were readily recognizable, it does not follow that the solution to those problems would have been obvious to one possessing ordinary skill in the art." *Woodstream Corp. v. Herter's, Inc.*, 170 USPQ 380, 387 (8th Cir. 1971).

Although the level of skill in the biotechnology arts may be relatively high, the person of ordinary skill is one who (by definition) is not "ingenious" (to use Wassenegger's term). In asserting that the present invention was merely a matter of carrying out modified Northern blots, the Examiner is ignoring the fact that the workers had (as a question of historical fact) been carrying out unmodified Northern blots while investigating PTGS for several years before the invention.

Thus a crucial element which was missing in the prior art in the present case was a reasonable expectation of success in detecting the entirely hypothetical molecules using e.g. Northern blotting. Indeed the more years which passed from the original 1992 and 1993 disclosures discussed above, the more entrenched this perception would have become.

"...A person of ordinary skill in the art is also presumed to be one who thinks along the line of conventional wisdom and is not one who undertakes to innovate, whether by patient, systematic research or extraordinary insights, it makes no difference which. *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454 [227 USPQ 293, 297-98] (Fed. Cir. 1985); see *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1449-54 [223 USPQ 603, 610-14] (Fed. Cir. 1984).

Thus although one of ordinary skill in the art is well able to practice the invention in the light of the applicant's

disclosure, this does not mean that it was obvious on the basis of the prior art that they could do so.

"At best, the examiner's comments regarding obviousness amount to an assertion that one of ordinary skill in the relevant art would have been able to arrive at appellant's invention because he had the necessary skills to carry out the requisite process steps. This is an inappropriate standard for obviousness. . . . That which is within the capabilities of one skilled in the art is not synonymous with obviousness. . . ." *Ex parte Levengood*, 28 USPQ2d 1300, 1301-02 (BPAI 1993) (citations omitted).

(4) Objective evidence of non-obviousness

As was pointed out in earlier responses, the assertion in the final rejection that Dougherty (1995) provided the motivation to modify Waterhouse (1998) and Wassenegger (1998) is absolutely contradicted by the dates of the relevant publications. Dougherty was published in 1995, which is 3 years before Waterhouse and Wassenegger. What's more those authors were clearly aware of Dougherty because it is cross-referenced in both Wassenegger [17 therein] and Waterhouse [19 therein].

Indeed Waterhouse (1998) actually includes analysis of mRNA (Fig 3) and Northern blots (Fig 5). Thus the evidence that the claimed invention is not *prima facie* obvious is found in the historical fact that the authors of these papers, while being aware of Dougherty (1995), and in spite of it being an art-recognized goal, did not in fact arrive at the invention.

It is established law that:

""[W]ide-spread recognition and use of the invention indicated that it would not have been obvious." *Windsurfing Int'l v. AMF Inc.*, 228 USPQ 562, 565 (CAFC 1986) (quoting *Windsurfing Int'l v. AMF Inc.*, 227 USPQ 927, 938-39 (S.D.N.Y. 1985)).

Following the publication of Hamilton & Baulcombe (1999) [in *Science* 286, 29 October: 950-952, already in proceedings] of the existence, nature and detectability of SRMs, there has been considerable interest in this technology.

One example of this is an article by Elbashir which appeared in *Nature*, 2001. On page 494 the authors state:

"The mediators of sequence-specific messenger RNA degradation are 21-22- nucleotide small interfering RNAs...(5-9)"

Reference 5 (the earliest of these) is Hamilton and Baulcombe (1999). Interestingly Elbashir et al. filed their own patent application after the present application was filed, and this is included for completeness (WO 01/75164).

Waterhouse et al. recently published an article in *TIPS*, 2001 entitled "Role of short RNAs in gene silencing"

On page 297 the authors state:

"The involvement of short RNAs in PTGS was **uncovered** when ~25 nt RNAs with sequence homology to a transgene were **detected** only in plants where the corresponding transgene was silenced (**3**)" (emphasis added).

Reference 3 is Hamilton and Baulcombe (1999).

Thus even Waterhouse (who's earlier reference forms the basis of the USC103 allegation) clearly acknowledges that it was the **actual detection** of SRMs by the present inventors which uncovered their involvement in PTGS.

(5) Conclusions under USC103

To establish obviousness under section 103,

"[b]oth the suggestion and the expectation of success must be founded on the prior art and not in applicant's disclosure." In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ 1529, 1531 (Fed. Cir. 1988).

A fair reading of the prior art shows that it could not reasonably have been expected that one of ordinary skill in the art could have **detected** SRMs.

Firstly the prior art was justifiably cautious about the existence of RNA-mediators of PTGS, using such terms as "hypothetical", "elusive", "models", "speculate" etc. (see sections quoted above).

Secondly, the prior art stated that even if RNA-mediators of PTGS existed, their detection was likely to prove problematic. For example Wassenneger refers to the requirement for "ingenious" experiments; English et al. (1996) state that detection would be "difficult"; Kunz et al. (1996) refer to their possible degradation and so on.

To quote *Ex parte Obukowicz*:

"At best the [prior art] statement is but an invitation to scientists to explore a new technology that seems a promising field of experimentation. The [prior art]


statement is of the type that gives only general guidance and is not at all specific as to the particular form of the claimed invention and how to achieve it. Such a suggestion may make an approach 'obvious to try' but it does not make the invention obvious." *Ex parte Obukowicz*, 27 USPQ2d 1063, 1065 (BPAI 1993).

Finally it is clear from the prior art that it was the actual detection of the existence of these hypothetical molecules which was required to revolutionize the understanding of gene regulation (Dougherty & Parkes, 1995). This is precisely what the present inventors did, as has been attributed to them by subsequent authors.

In view of the evidence presented herewith and the foregoing remarks, it is respectfully urged that all of the objections and rejections set forth in the December 4, 2001 Official Action be withdrawn, and that this application be passed to issue and such action is earnestly solicited.

Respectfully submitted,

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Enclosures: -Certified Copy of Priority Document
 -Declaration by Drs. Hamilton and Baulcombe
 -Supplemental Information Disclosure Form and PTO
 1449 form
 -Abstract of subject matter presented at Leysin,
 Switzerland